Overgrowth Syndromes

Andrew C. Edmondson[1] Jennifer M. Kalish[1]

[1] Division of Human Genetics, Children's Hospital of Philadelphia and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, United States

J Pediatr Genet 2015;4:136–143.

Address for correspondence Jennifer M. Kalish, MD, PhD, Division of Human Genetics, Children's Hospital of Philadelphia and the Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, ARC 1002, 3615 Civic Center Boulevard, Philadelphia, PA 19104, United States (e-mail: KALISHJ@email.chop.edu).

Abstract

Numerous multiple malformation syndromes associated with pathologic overgrowth have been described and, for many, their molecular bases elucidated. This review describes the characteristic features of these overgrowth syndromes, as well as the current understanding of their molecular bases, intellectual outcomes, and cancer predispositions. We review syndromes such as Sotos, Malan, Marshall–Smith, Weaver, Simpson–Golabi–Behmel, Perlman, Bannayan–Riley–Ruvalcaba, PI3K-related, Proteus, Beckwith–Wiedemann, fibrous dysplasia, Klippel–Trenaunay–Weber, and Maffucci.

Keywords
- overgrowth syndrome
- Sotos
- Malan
- Marshall–Smith
- Simpson–Golabi–Behmel
- Perlman
- Bannayan–Riley–Ruvalcaba
- PI3K-related
- Proteus
- Beckwith–Wiedemann

Introduction

About 5% of all newborns have a birth weight greater than 4,000 g, known as macrosomia.[1] Although maternal diabetes or neonatal hyperinsulinism may contribute to neonatal macrosomia, excessive birth weight frequently represents a normal variation influenced by family history, excessive maternal weight gain during pregnancy, maternal multiparous state, male fetal sex, higher maternal socioeconomic status,[2] familial tall stature, and familial rapid maturation.[1] In contrast, pathologic overgrowth may be of prenatal or postnatal onset. It may result from an increased number of cells (intrinsic cellular hyperplasia), hypertrophy of the normal number of fetal cells, an increase in interstitial spaces, or a combination of all these.[1]

Numerous multiple malformation syndromes associated with growth excess have been described. These pathologic syndromes share several characteristics: the overgrowth is present at birth and persists into postnatal life, affects both weight and length, and is associated with multiple characteristic anomalies, sometimes with mental deficiency, and often with a neoplastic predisposition.[2,3] This review describes the

received
May 15, 2015
accepted after revision
May 20, 2015
published online
September 25, 2015

Issue Theme Genetic Advances in Intellectual Disability; Guest Editor: Donatella Milani, MD

DOI http://dx.doi.org/10.1055/s-0035-1564440.
ISSN 2146-4596.

characteristic features of the most common overgrowth syndromes, as well as the current understanding of their molecular bases, intellectual outcomes, and cancer predispositions. In this review, overgrowth syndromes are grouped by their underlying genetic mechanisms as constitutional syndromes, somatic syndromes, and syndromes for which there is no identified genetic etiology.

Sotos-Like Syndromes

Sotos syndrome has an estimated incidence of 1:14,000 live births.[4] This syndrome is characterized by increased birth weight and length, with excessive growth during the first 4 years and an advanced bone age. Disproportionately long limbs cause much of the increased length.[2] Children with Sotos syndrome have distinctive facial features with macrodolichocephaly, marked frontal bossing, and a frontoparietal receding hairline. Bitemporal narrowing gives the appearance of hypertelorism, and the palpebral fissures are typically down slanting. The face is long and thin with a prominent long and narrow inferior mandible.[5]

Just over 10% of patients with Sotos syndrome have congenital heart defects, usually a patent ductus arteriosus (PDA) or atrial septal defect.[6] Renal abnormalities and scoliosis have also been frequently reported.[5] Sotos syndrome is associated with dilatation of the cerebral ventricles and other brain formation abnormalities, including an absent corpus callosum, prominent cortical sulci, trigone, occipital horns, cavum septum pellucidum, and cavum velum interpositi.[6,7] Approximately 50% of individuals with Sotos syndrome experience seizures.[2]

Mutations of the gene encoding nuclear receptor-binding SET domain-containing protein 1 (NSD1) are found in approximately 90% of patients.[5] Sotos syndrome results from constitutional intragenic loss-of-function mutations,[8] primarily truncating mutations,[9] and, in the Japanese population, whole gene deletions[10] of NSD1, which lead to germline haploinsufficiency. NSD1 is a SET domain-containing histone methyltransferase that preferentially methylates lysine residue 36 of histone 3 (H3K36), which is primarily associated with active transcription.[5]

Children with Sotos syndrome can display neonatal hypotonia with early feeding difficulties, as well as delays in motor development and expressive language, often not walking until after 15 months or talking until after 2.5 years. Children may show nonprogressive neurologic dysfunction with clumsiness and poor coordination.[11] Most individuals (97%) carrying an *NSD1* mutation have intellectual disabilities, ranging from mild (~30%) to moderate (~45%) or severe (~20%).[9]

Somatic mutations of the protooncogene *NSD1* have been identified in multiple tumor types. These mutations include a recurrent cryptic t(5;11)(q35.3;p15.5) translocation in approximately 5% of childhood acute myeloid leukemia cases,[12] somatic epigenetic silencing of *NSD1* through promoter hypermethylation in neuroblastoma and glioma,[13] and somatic *NSD1* mutations in carcinoma of the upper airway and digestive tract.[5] As *NSD1* presumably functions as a tumor suppressor gene, individuals with Sotos syndrome are expected to be at an increased risk for a "second hit" resulting in increased risk of tumor formation.[1] Despite this theoretical risk, only approximately 3% of individuals with Sotos syndrome develop tumors, which include neuroblastoma, sacrococcygeal teratoma, presacral ganglioneuroma, acute lymphocytic leukemia, and small-cell lung cancer.[9] As the tumor risk is small, and there are currently no effective screening modalities for the tumor types observed in Sotos syndrome, cancer screening is not recommended.[5]

The most recently described overgrowth syndrome, Malan syndrome, has similar physical characteristics to Sotos syndrome but has a different underlying genetic basis. Researchers searching for molecular causes of unexplained syndromic overgrowth screened 18 overgrowth patients with nonconsanguinity, developmental delay, height above the 95th percentile, and/or macrocephaly and patients with at least two of the following: advanced bone age, dysmorphic craniofacial features, and congenital malformations with array comparative genomic hybridization. Through this analysis, they identified nuclear factor I/X (*NFIX*) as a candidate gene. Subsequent screening of *NFIX* in 76 individuals with unexplained syndromic overgrowth identified 3 individuals who initially had been diagnosed with a Sotos-like phenotype.[14] Identification of additional cases allowed further characterization of the phenotype, which includes neonatal hypotonia and feeding difficulties, postnatal overgrowth, macrocephaly, advanced bone age, dysmorphic features (long narrow face with a high forehead), pectus excavatum, scoliosis, ocular findings (strabismus, nystagmus, optic disc pallor/hypoplasia), and developmental delay.[15]

Malan syndrome appears to arise from mutations leading to haploinsufficiency of *NFIX*.[14] NFIX is a transcription factor in the nuclear factor one (NFI) family, which is important in replication, signal transduction, and transcriptional processes, but the exact genes regulated by *NFIX* have yet to be elucidated. Moderate developmental delay, including autism (~25% of cases), has been demonstrated in all reported cases of Malan syndrome.[15] Approximately 25% of patients with Malan syndrome have seizures,[15] but there have been no reports of cancer with this syndrome.[15]

Marshall–Smith syndrome is allelic to Malan syndrome. Its incidence is unknown due to its rarity. Characteristics include accelerated osseous maturation, dysmorphic features (prominent forehead, bushy eyebrows, bulging eyes), and large hands and feet. Individuals with Marshall–Smith syndrome frequently have failure to thrive, chronic respiratory distress, and short lifespan.[16] Dominant-negative mutations in *NFIX* underlie the syndrome.[14,17] Individuals with this syndrome have moderate to severe mental deficiency and major developmental delays,[14] with many dying as infants. Although the rarity of the disorder precludes identification of an increased cancer risk, one case of Wilms tumor coexisting with Marshall–Smith syndrome has been reported.[14]

Weaver Syndrome

Owing to the many similar features between the two, Weaver syndrome is often included in the differential diagnosis of

Sotos syndrome. Weaver syndrome is characterized by prenatal-onset overgrowth with accelerated osseous maturation, widened distal long bones, camptodactyly, and a distinctive craniofacial appearance. Individuals with Weaver syndrome have macrocephaly; a broad forehead; a flattened occiput with large ears that may be mildly dysplastic and low set; true hypertelorism; a long prominent philtrum; relative micrognathia; soft, loose skin with redundant nuchal skin folds; umbilical hernia; and thin, deep-set nails.[5] Skeletal growth is more accelerated than osseous maturation, resulting in excessive adult height.[2] Individuals may have congenital heart defects, such as ventricular septal defect and PDA.[18] Brain anomalies include cysts of the septum pellucidum, cerebral atrophy, and pachygyria.[2] There is a broad phenotypic spectrum for Weaver syndrome, making true incidence estimates difficult.[19]

Constitutional mutations of enhancer of zeste, drosophila, homolog 2 (*EZH2*) have been implicated in Weaver syndrome. Most of these mutations are missense or unlikely to cause simple haploinsufficiency, obscuring the pathogenic mechanism for Weaver syndrome.[20] EZH2 is a SET domain-containing histone methyltransferase; however, in contrast to NSD1, it shows specificity for lysine residue 27 (H3K27), which is associated with transcriptional repression.[5]

Mild tone abnormalities and motor development delays are common in Weaver syndrome. Approximately 18% of individuals with mutations of *EZH2* have no reported intellectual disability; the remainder show intellectual disabilities ranging from mild (~45%) to moderate (26%) or severe (5%).[21] Somatic disruption of *EZH2* is important in the development of many tumors, particularly hematopoietic malignancies,[22] with both activating and inactivating mutations associated with tumorigenesis.[5,23,24] Approximately 5% of individuals with Weaver syndrome develop tumors, such as lymphoma, acute lymphoblastic leukemia, neuroblastoma, and sacrococcygeal teratoma.[21,25] However, as with Sotos syndrome, routine cancer screening is not recommended.[5]

Simpson–Golabi–Behmel Syndrome

Simpson–Golabi–Behmel syndrome is characterized by prenatal and postnatal overgrowth. Individuals have coarse facial features, hypertelorism, down slanting palpebral fissures, epicanthic folds, a short nose with a broad nasal bridge, macrostomia, macroglossia, a central groove of the lower lip and/or tongue (frequently with eversion of the lower lips), and, occasionally, cleft lip and palate.[2,26] Short and broad hands and feet show metatarsus varus, talipes equinovarus, fingernail hypoplasia of the index finger, cutaneous syndactyly, and postaxial polydactyly. Supernumerary nipples are a frequent finding. Organomegaly of the liver, spleen, and kidneys is common, with multicystic dysplasia of the kidneys. Lung segmentation defects and diaphragmatic defects have been reported. Cardiac abnormalities are found in 36 to 47% of patients.[27] Gastrointestinal manifestations—including malrotation, pyloric ring, and Meckel diverticulum—have been described. Skeletal findings include vertebral segmentation defects, such as C2–C3 fusion, cervical ribs, six lumbar vertebrae, sacrococcygeal defects, and scoliosis.[2] Malformations of the central nervous system are rare, but there have been reports of partial agenesis of the corpus callosum with agenesis of the septum pellucidum and bilateral ventriculomegaly,[28] arrhinencephaly, a thin corpus callosum, lipoma of the floor of the third ventricle, and hydrocephalus.[26]

Simpson–Golabi–Behmel syndrome is an X-linked disorder caused by constitutional mutations in the glypican 3 (*GPC3*) gene that encodes a heparin sulfate proteoglycan.[26] One large case series of patients with this disorder found 38% exonic deletions, 24% frameshift mutations, 17% nonsense mutations, 17% missense mutations, and 3% exonic duplications in the gene, without an obvious correlation between genotype/phenotype and the mutation or type of mutation.[26]

Despite the multiple congenital anomalies present in Simpson–Golabi–Behmel syndrome, mental development has been often reported as normal.[29] A recent review suggested that individuals have neonatal hypotonia with some mild delays in milestones, sitting independently at 8.5 months and walking independently at 16 months.[26] They may experience speech difficulties, most frequently caused by macroglossia and/or cleft palate.[26] However, less than half of patients had intellectual disabilities and, when present, they were typically mild and not associated with developmental delays.[26] Tumors, usually of renal origin, occur in roughly 8 to 10% of individuals with this syndrome.[26,30,31] Hepatoblastoma[32] and one case of leukemia[26] have also been reported. Tumor screening with abdominal ultrasounds to identify renal tumors and α-fetoprotein (AFP) testing to identify hepatic tumors have been proposed.[2]

Perlman Syndrome

Perlman syndrome is characterized by neonatal macrosomia, polyhydramnios, a characteristic facial dysmorphology (broad and flat nasal bridge, everted V-shaped upper lip, low-set ears, deep-set eyes, prominent forehead[33]), renal dysplasia, nephroblastomatosis, and multiple congenital anomalies. Abdominal dystocia due to visceromegaly, typically involving the heart, liver, spleen, pancreas, and kidneys, has been reported.[2] Male cryptorchidism is also common.[33] There is a high neonatal mortality rate (>50%) in the first month of life,[33] and growth parameters of surviving infants are at the lower limits of normal.[2] Infants with Perlman syndrome exhibit severe hypotonia.[33] Agenesis of the corpus callosum has been reported.[34]

Constitutional mutations of DIS3-like exonuclease 2 (*DIS3L2*), a homolog of the *Schizosaccharomyces pombe dis3* gene, have been reported in Perlman syndrome.[35] Dis3 is a component of the yeast core RNA exosome complex and is responsible for its 3′- to 5′-exoribonuclease activity.[36] *DIS3L2* regulates mitosis and cell proliferation. Loss of the regulatory mechanisms of *DIS3L2* in Perlman syndrome is thought to underlie the increased tumor risk through increased cell proliferation.[35]

Moderate developmental delay has been reported in patients with Perlman syndrome.[37,38] Furthermore, approximately 67% of children with Perlman syndrome who survive

beyond the neonatal period develop Wilms tumors, which occur at an earlier age than sporadic cases and are frequently bilateral.[39] Approximately 30% of sporadic Wilms tumors are expected to harbor mutations or deletions of *DIS3L2*.[35]

Bannayan–Riley–Ruvalcaba Syndrome

Developmental delay and macrocephaly are hallmark features of Bannayan–Riley–Ruvalcaba syndrome (BRRS),[40] which is characterized by cutaneous lesions (pigmented macules on the penis and cafe-au-lait spots), vascular malformations, lipomas, hamartomatous polyps of the distal ileum and colon, and Hashimoto thyroiditis.[2,40,41] Hemangiomas have traditionally been associated with BRRS.[40] Infants are typically macrosomic, with birth lengths above the 97th percentile. Subsequent growth deceleration results in normalization of all growth parameters except macrocephaly.[2]

BRRS is one of several syndromes associated with phosphatase and tensin homolog on chromosome 10 (PTEN), with high phenotypic overlap among these syndromes. Consequently, the terms *PTEN hamartoma tumor syndrome* and *PTEN-opathies* have been used to describe any patient with germline *PTEN* mutations, regardless of the phenotype.[41] Wild-type PTEN regulates the cell cycle, cell migration, and apoptosis via the canonical *PI3K/AKT/mTOR* pathway. Lack of normal *PTEN* leads to increased cell migration and cell survival secondary to upregulation of the AKT and MAPK pathways.[41] PTEN has broad downstream and interacting networks, and patients with mutations in other genes along this pathway demonstrate features overlapping with PTEN-opathies.[41]

Up to 17% of children with macrocephaly and autism without other BRRS features may have germline *PTEN* mutations. Thus, it is recommended that all macrocephalic children with autism or developmental delay be tested for *PTEN* mutations.[42,43] Hypotonia, gross motor delay, mild to severe mental deficiency, and speech delay are reported in approximately 70% of BRRS patients. Greater than 25% of BRRS patients have experienced seizures.[2] Lifetime cancer risks for any individual carrying a constitutional *PTEN* mutation are greater than population norms. Breast, thyroid, renal, and endometrial cancers are the predominant cancer types, although colorectal cancer and melanoma are increasingly being reported. Patients with constitutional *PTEN* mutations are encouraged to undergo frequent cancer screenings for early tumor detection.[44]

Beckwith–Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is characterized by macrosomia, asymmetric overgrowth (hemihyperplasia), macroglossia, abdominal wall defects (umbilical hernia, omphalocele, diastasis recti), hypoglycemia, ear creases, visceromegaly, renal malformations, facial nevus flammeus, and embryonal tumors[45] (►**Fig. 1**). Its heterogeneous clinical presentation has led some to suggest renaming BWS as "11p overgrowth spectrum" on the basis of the molecular etiology, one extreme of which would be the classically described BWS.

The molecular etiology is complex and involves epigenomic and genomic alterations in the imprinting clusters on chromosome 11p15. These changes are detected in up to 80% of classic BWS patients,[46] but less often in isolated hemihyperplasia patients. The 11p15 chromosomal region is divided into two distinct regulatory domains. The distal domain contains the imprinted genes insulin-like growth factor 2 (*IGF2*) and the long noncoding RNA *H19* near imprinting center 1 (IC1), which is a differentially methylated region, methylated on the paternal allele.[45] The proximal domain including imprinting center 2 (IC2) spans a 1-Mb region containing the imprinted genes, including a paternally expressed noncoding RNA (*KCNQ1OT1*) and maternally expressed gene encoding a cyclin-dependent kinase inhibitor (*CDKN1C*).[45] Imprinting defects at IC2 account for 50% of the molecular defects in BWS patients.[46] Approximately 20% of BWS cases have paternal uniparental disomy (pUPD) involving chromosome 11p15, which encompasses both imprinted gene clusters.[45] BWS cases with pUPD exhibit somatic mosaicism.[45]

Individuals with BWS largely have normal intelligence and developmental outcomes. Adverse developmental outcomes are generally attributable to complications of prematurity or extreme hypoglycemia, rather than the syndrome itself.[2] The exception is BWS caused by duplications of paternal chromosome 11p15, which can be associated with moderate to severe intellectual disability and distinct dysmorphic features.[47]

Children with BWS have an increased risk (~8.6%) of developing embryonal tumors.[48] The most common tumor type is Wilms tumor, although hepatoblastoma, neuroblastoma, ganglioneuroma, adrenocortical carcinoma, rhabdomyosarcoma, acute lymphoid leukemia, liver sarcoma, thyroid carcinoma, and melanoma have been reported.[45,48,49] In BWS, tumor risk appears to be related to the underlying defect.[49] Patients with IC1 methylation alterations and pUPD11 have the highest risk.[46,48,49] Tumor screening is recommended in BWS, with serum AFP measurements until age 4 years and abdominal ultrasounds until age 8 years.[50]

PI3K-Related Syndromes

PI3K-related megalencephaly syndromes include megalencephaly–polymicrogyria–polydactyly–hydrocephalus (MPPH) and megalencephaly–capillary malformation (MCAP). These brain overgrowth disorders are characterized by congenital or early postnatal megalencephaly, often with progressive ventriculomegaly (leading to hydrocephalus), cerebellar tonsillar ectopia (leading to Chiari malformation), and cortical brain abnormalities (polymicrogyria). MPPH and MCAP can be distinguished by the characteristic features of MCAP, which include cutaneous capillary vascular malformations, finger or toe syndactyly, postaxial polydactyly, and mild focal or segmental somatic overgrowth.[51] In contrast, there are no consistent dysmorphic features in MPPH, and the observed

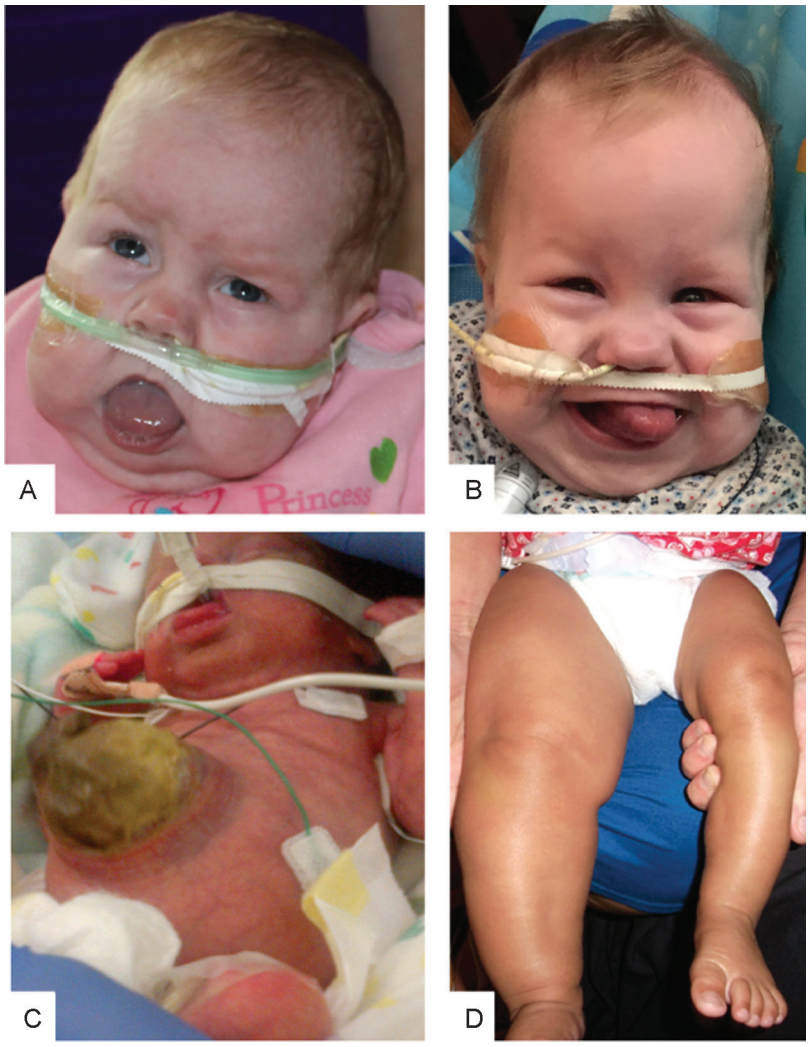

Fig. 1 Clinical features of patients with Beckwith–Wiedemann syndrome (BWS). (A, B) BWS patient with macroglossia at 6 months and 14 months of age, respectively. (C) BWS patient with omphalocele. (D) BWS patient with severe hemihyperplasia.

abnormal facial features (prominent forehead, low nasal bridge, apparent hypertelorism) are likely secondary to the megalencephaly. Postaxial polydactyly is reported in less than half of MPPH individuals.[51] Individuals with MPPH and MCAP frequently have seizures with varying degrees of controllability by antiepileptics.

MPPH is believed to be caused by de novo germline mutations in PIK3R2, AKT3, and, potentially, cyclin D2 (*CCND2*), whereas MCAP is caused by postzygotic, mosaic, and rare germline mutations in *PIK3CA*.[51] PIK3R2, AKT3, and PIK3CA are members of the phosphatidylinositol-3-kinase (PI3K)-v-akt murine thymoma viral oncogene homolog (AKT) pathway, which is critical for proliferation, cell growth, and apoptosis. Identified mutations in these three genes typically lead to activation of the *PI3K-AKT* pathway.[51] *PIK3R2* encodes the p85b regulatory subunit of class IA PI3K enzymatic complex and mediates activation of class IA PI3K by receptor tyrosine kinases. All PI3K mutation-positive MPPH individuals carry the same PIK3R2 mutation (p.Gly373Arg), located within the Src-homology 2 (SH2) domain of p85b.[51] This mutation has been shown to result in increased *PI3K* activity.[52] *CCND2* mutations appear to stabilize cyclin D2, a downstream target of the *PI3K*-mediated tyrosine kinases. The resulting accumulation of cyclin D2 is a unifying mechanism in *PI3K-AKT*-related megalencephaly syndromes.[53]

Several other overgrowth syndromes are caused by postzygotic mutations in *PIK3CA*. These syndromes are characterized by patchy segmental overgrowth and the associated anomalies of the *C*ongenital, *L*ipomatous, *O*vergrowth, *V*ascular malformations, *E*pidermal nevi, and *S*pinal/skeletal anomalies and/or scoliosis (CLOVES) phenotypic spectrum.[54] The timing and tissue location of the mutation may help explain the phenotypic variability of these overgrowth syndromes, although investigations so far have not shown correlation of the mutational load in affected tissues with either the quality or overall severity of the physical manifestations.[54]

Individuals with MPPH and MCAP typically have developmental delays. In one case series of these patients, only one individual was reported to be developmentally normal. Other individuals have delays ranging from mild to severe,[55] as well as autistic features, unexplained irritability, attention deficit

hyperactivity disorder, and obsessive compulsive disorder.[55] Almost all individuals on the CLOVES spectrum without brain involvement have normal developmental milestones and cognitive abilities.[56]

Somatic mutations in *P13KCA* are seen in many cancers, including glioblastoma and colorectal, ovarian, breast, and hepatocellular carcinomas.[56] MCAP and MPPH may have lower tumor risks than patients with other overgrowth syndromes. Nevertheless, Wilms tumor, meningioma, and leukemia have been reported in MCAP patients,[55] and medulloblastoma was reported in one patient with MPPH.[57] Wilms tumor was reported in one individual on the CLOVES spectrum.[54] Current cancer screening recommendations are based on those for BWS.[56]

Proteus Syndrome

Proteus syndrome is characterized by asymmetric overgrowth with skeletal defects, epidermal nevi, vascular malformations, dysregulated adipose tissue, and pulmonary abnormalities. While not an obligatory finding, the presence of cerebriform connective tissue nevi is nearly pathognomonic for Proteus syndrome. Nevi are most frequently identified on the foot plantar surfaces, but have also been observed on the hands, abdomen, chest, and nose.[58] About 10% of patients with Proteus syndrome experience seizures.

Proteus syndrome is caused by somatic mutations in *AKT1*, explaining the variety of phenotypic features. A single mutation in *AKT1*, c.49G→A, p.Glu17Lys, which causes constitutive activation of AKT1 through Ser473 and Thr308 phosphorylation,[59] has been identified in individuals with Proteus syndrome.[60]

Most individuals with Proteus syndrome seem to have normal intelligence, although approximately 20% of cases have some degree of mental deficiency. Mental deficiency and seizures are much more likely if there is brain involvement or brain malformations.[2] The specific *AKT1* mutation causative of Proteus syndrome has been reported in some tumors, including breast, thyroid, genitourinary tract, lung, and endometrial cancers.[60] However, only lipomas are common in Proteus syndrome. Other reported neoplasms include adenoma of the parotid gland, cystadenoma of the ovary, testicular tumor, meningioma, and mesothelioma.[58]

Fibrous Dysplasia

Fibrous dysplasia (FD) is a skeletal overgrowth disorder with a broad spectrum of clinical expression, ranging from asymptomatic radiographic findings at a single skeletal site to disabling disease. FD may involve one bone (monostotic forms), multiple bones (polyostotic FD), or the entire skeleton (panostotic FD). McCune–Albright syndrome is a polyostotic FD with cutaneous pigmentation and endocrinopathy, including precocious puberty, hyperthyroidism, growth hormone excess, and Cushing syndrome.[61] Bone pain, fracture, and deformity are the most common presenting features. Although any bone may be affected, the skull base and proximal metaphysis of the femora are the most commonly involved sites. Overgrowth of the craniofacial bone can result in severe deformity, beginning with facial asymmetry or a persistent bump and progressing with expansion of malar prominences or frontal bossing into major disfiguration in adulthood.[61] Bony overgrowth in FD can lead to cranial nerve entrapment, deafness, vestibular dysfunction, and seizures.[62]

FD is caused by activating missense mutations in the guanine nucleotide binding protein, α stimulating (*GNAS1*) gene, which encodes the α subunit of the stimulatory G-protein, Gsα. Mutations occur somatically and result in mosaicism, explaining the extreme heterogeneity of the condition. The extent and severity of disease are related to the timing of the mutational event during development and the severity of the mutation.[61] Individuals with FD are typically developmentally normal and malignancy is rare (~1%), with osteogenic sarcoma being the most common cancer seen in FD.[61]

Klippel–Trenaunay–Weber Syndrome

Klippel–Trenaunay–Weber syndrome is characterized by capillary malformations associated with venous malformations consisting of arteriovenous fistulas with bone or tissue hypertrophy in the affected limb. The most common manifestation, present in 98% of patients, is capillary malformation, represented by cutaneous hemangiomas or port-wine stains. Limb hypertrophy is typical when the limb is affected by capillary malformations; these malformations rarely cross the midline.[63] The lower limbs are much more commonly affected than the upper limbs. There is currently no known genetic cause of Klippel–Trenaunay–Weber syndrome, although a somatic mosaic mutation has been postulated.[64] Developmental outcomes are typically normal, and there is no known cancer predisposition.

Maffucci Syndrome

Maffucci syndrome is characterized by multiple enchondromas and noncancerous cartilaginous growths on the limb bones. These growths primarily occur on the hands and feet, but have also been reported on the skull, ribs, and vertebrae. Enchondromas occur asymmetrically and result in severe bone deformities, limb shortening, fractures, and short stature.[2] Individuals with Maffucci syndrome have venous malformations, capillary hemangiomas, and, occasionally, lymphangiomas. They are typically born normal and subsequently develop enchondromas.

There is currently no known genetic cause of this syndrome. Individuals with Maffucci syndrome are of normal intelligence and achieve normal developmental milestones. Enchondromas may undergo malignant transformation and become chondrosarcomas (transformation rate: 17–30%[2]). Angiosarcoma, fibrosarcoma, pancreatic carcinoma, hepatic adenocarcinoma, ovarian cystadenocarcinoma, teratoma, glioma, astrocytoma, and pituitary adenoma have also been reported.[2]

Conclusion

The overgrowth syndromes comprise a diverse group of clinically recognizable multiple congenital malformation

syndromes. Recent elucidation of the genetic bases for many of these syndromes provides insight into the normal regulation of growth and development. Intellectual outcomes vary greatly among the syndromes. Once diagnosed, individuals with overgrowth syndromes should be regularly followed up to ensure optimal developmental outcomes. Some of the disorders have elevated risk of neoplasm development, and there are recommended clinical cancer screening algorithms in place. We hope this review will provide a context for recognizing overgrowth syndromes such that appropriate developmental follow-up and tumor screening can be instituted in a timely manner.

Acknowledgments

J. M. K. is supported by the National Institutes of Health and the Alex's Lemonade Stand Foundation. The authors thank Kathryn Kadash-Edmondson for critical reading of the manuscript.

References

1 Stevenson RE, Hall JG. Human Malformations and Related Anomalies. Third edition, ed. Oxford; New York: Oxford University Press; 2015
2 Cohen MM, Neri G, Weksberg R. Overgrowth Syndromes. New York: Oxford University Press; 2002
3 Cohen MM Jr. Mental deficiency, alterations in performance, and CNS abnormalities in overgrowth syndromes. Am J Med Genet C Semin Med Genet 2003;117C(1):49–56
4 Tatton-Brown K, Cole TRP, Rahman N. Sotos syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., eds. GeneReviews(R). Seattle, WA; 1993. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1116/. Accessed May 5, 2015
5 Tatton-Brown K, Rahman N. The NSD1 and EZH2 overgrowth genes, similarities and differences. Am J Med Genet C Semin Med Genet 2013;163C(2):86–91
6 Gusmão Melo D, Pina-Neto JM, Acosta AX, Daniel J, de Castro V, Santos AC. Neuroimaging and echocardiographic findings in Sotos syndrome. Am J Med Genet 2000;90(5):432–434
7 Schaefer GB, Bodensteiner JB, Buehler BA, Lin A, Cole TR. The neuroimaging findings in Sotos syndrome. Am J Med Genet 1997; 68(4):462–465
8 Kurotaki N, Imaizumi K, Harada N, et al. Haploinsufficiency of NSD1 causes Sotos syndrome. Nat Genet 2002;30(4):365–366
9 Tatton-Brown K, Douglas J, Coleman K, et al; Childhood Overgrowth Collaboration. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with NSD1 aberrations. Am J Hum Genet 2005;77(2):193–204
10 Kamimura J, Endo Y, Kurotaki N, et al. Identification of eight novel NSD1 mutations in Sotos syndrome. J Med Genet 2003;40(11): e126
11 Cohen MM Jr. Overgrowth syndromes: an update. Adv Pediatr 1999;46:441–491
12 Cerveira N, Correia C, Dória S, et al. Frequency of NUP98-NSD1 fusion transcript in childhood acute myeloid leukaemia. Leukemia 2003;17(11):2244–2247
13 Berdasco M, Ropero S, Setien F, et al. Epigenetic inactivation of the Sotos overgrowth syndrome gene histone methyltransferase NSD1 in human neuroblastoma and glioma. Proc Natl Acad Sci U S A 2009;106(51):21830–21835
14 Malan V, Rajan D, Thomas S, et al. Distinct effects of allelic NFIX mutations on nonsense-mediated mRNA decay engender either a Sotos-like or a Marshall-Smith syndrome. Am J Hum Genet 2010; 87(2):189–198
15 Klaassens M, Morrogh D, Rosser EM, et al. Malan syndrome: Sotos-like overgrowth with de novo NFIX sequence variants and deletions in six new patients and a review of the literature. Eur J Hum Genet 2015;23(5):610–615
16 Marshall RE, Graham CB, Scott CR, Smith DW. Syndrome of accelerated skeletal maturation and relative failure to thrive: a newly recognized clinical growth disorder. J Pediatr 1971;78(1): 95–101
17 Schanze D, Neubauer D, Cormier-Daire V, et al. Deletions in the 3′ part of the NFIX gene including a recurrent Alu-mediated deletion of exon 6 and 7 account for previously unexplained cases of Marshall-Smith syndrome. Hum Mutat 2014;35(9):1092–1100
18 Huffman C, McCandless D, Jasty R, et al. Weaver syndrome with neuroblastoma and cardiovascular anomalies. Am J Med Genet 2001;99(3):252–255
19 Tatton-Brown K, Rahman N. EZH2-Related Overgrowth. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., eds. GeneReviews(R). Seattle, WA; 1993. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1116/. Accessed May 5, 2015
20 Tatton-Brown K, Hanks S, Ruark E, et al; Childhood Overgrowth Collaboration. Germline mutations in the oncogene EZH2 cause Weaver syndrome and increased human height. Oncotarget 2011; 2(12):1127–1133
21 Tatton-Brown K, Murray A, Hanks S, et al; Childhood Overgrowth Consortium. Weaver syndrome and EZH2 mutations: clarifying the clinical phenotype. Am J Med Genet A 2013;161A(12): 2972–2980
22 Chase A, Cross NC. Aberrations of EZH2 in cancer. Clin Cancer Res 2011;17(9):2613–2618
23 Morin RD, Johnson NA, Severson TM, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. Nat Genet 2010;42(2):181–185
24 Ernst T, Chase AJ, Score J, et al. Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. Nat Genet 2010;42(8):722–726
25 Kelly TE, Alford BA, Abel M. Cervical spine anomalies and tumors in Weaver syndrome. Am J Med Genet 2000;95(5):492–495
26 Cottereau E, Mortemousque I, Moizard MP, et al. Phenotypic spectrum of Simpson-Golabi-Behmel syndrome in a series of 42 cases with a mutation in GPC3 and review of the literature. Am J Med Genet C Semin Med Genet 2013;163C(2):92–105
27 Lin AE, Neri G, Hughes-Benzie R, Weksberg R. Cardiac anomalies in the Simpson-Golabi-Behmel syndrome. Am J Med Genet 1999; 83(5):378–381
28 Pénisson-Besnier I, Lebouvier T, Moizard MP, et al. Carotid artery dissection in an adult with the Simpson-Golabi-Behmel syndrome. Am J Med Genet A 2008;146A(4):464–467
29 Neri G, Gurrieri F, Zanni G, Lin A. Clinical and molecular aspects of the Simpson-Golabi-Behmel syndrome. Am J Med Genet 1998; 79(4):279–283
30 Lapunzina P. Risk of tumorigenesis in overgrowth syndromes: a comprehensive review. Am J Med Genet C Semin Med Genet 2005; 137C(1):53–71
31 Hughes-Benzie RM, Hunter AG, Allanson JE, Mackenzie AE. Simpson-Golabi-Behmel syndrome associated with renal dysplasia and embryonal tumor: localization of the gene to Xqcen-q21. Am J Med Genet 1992;43(1-2):428–435
32 Lapunzina P, Badia I, Galoppo C, et al. A patient with Simpson-Golabi-Behmel syndrome and hepatocellular carcinoma. J Med Genet 1998;35(2):153–156
33 Morris MR, Astuti D, Maher ER. Perlman syndrome: overgrowth, Wilms tumor predisposition and DIS3L2. Am J Med Genet C Semin Med Genet 2013;163C(2):106–113
34 Henneveld HT, van Lingen RA, Hamel BC, Stolte-Dijkstra I, van Essen AJ. Perlman syndrome: four additional cases and review. Am J Med Genet 1999;86(5):439–446

35 Astuti D, Morris MR, Cooper WN, et al. Germline mutations in DIS3L2 cause the Perlman syndrome of overgrowth and Wilms tumor susceptibility. Nat Genet 2012;44(3):277–284
36 Dziembowski A, Lorentzen E, Conti E, Séraphin B. A single subunit, Dis3, is essentially responsible for yeast exosome core activity. Nat Struct Mol Biol 2007;14(1):15–22
37 Greenberg F, Stein F, Gresik MV, et al. The Perlman familial nephroblastomatosis syndrome. Am J Med Genet 1986;24(1): 101–110
38 Neri G, Martini-Neri ME, Katz BE, Opitz JM. The Perlman syndrome: familial renal dysplasia with Wilms tumor, fetal gigantism and multiple congenital anomalies. Am J Med Genet 1984;19(1): 195–207
39 Alessandri JL, Cuillier F, Ramful D, et al. Perlman syndrome: report, prenatal findings and review. Am J Med Genet A 2008;146A(19): 2532–2537
40 Gorlin RJ, Cohen MM Jr, Condon LM, Burke BA. Bannayan-Riley-Ruvalcaba syndrome. Am J Med Genet 1992;44(3):307–314
41 Mester J, Eng C. When overgrowth bumps into cancer: the PTEN-opathies. Am J Med Genet C Semin Med Genet 2013;163C(2): 114–121
42 Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013;15(5):399–407
43 McBride KL, Varga EA, Pastore MT, et al. Confirmation study of PTEN mutations among individuals with autism or developmental delays/mental retardation and macrocephaly. Autism Res 2010; 3(3):137–141
44 Tan MH, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18(2):400–407
45 Choufani S, Shuman C, Weksberg R. Molecular findings in Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet 2013;163C(2):131–140
46 Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Eur J Hum Genet 2010;18(1):8–14
47 Slavotinek A, Gaunt L, Donnai D. Paternally inherited duplications of 11p15.5 and Beckwith-Wiedemann syndrome. J Med Genet 1997;34(10):819–826
48 Brioude F, Lacoste A, Netchine I, et al. Beckwith-Wiedemann syndrome: growth pattern and tumor risk according to molecular mechanism, and guidelines for tumor surveillance. Horm Res Paediatr 2013;80(6):457–465
49 Mussa A, Russo S, De Crescenzo A, et al. (Epi)genotype-phenotype correlations in Beckwith-Wiedemann syndrome. Eur J Hum Genet 2015; Epub ahead of print. Doi: 10.1038/ejhg.2015.88
50 Tan TY, Amor DJ. Tumour surveillance in Beckwith-Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice. J Paediatr Child Health 2006;42(9):486–490
51 Mirzaa GM, Rivière JB, Dobyns WB. Megalencephaly syndromes and activating mutations in the PI3K-AKT pathway: MPPH and MCAP. Am J Med Genet C Semin Med Genet 2013;163C(2): 122–130
52 Rivière JB, Mirzaa GM, O'Roak BJ, et al; Finding of Rare Disease Genes (FORGE) Canada Consortium. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. Nat Genet 2012;44(8):934–940
53 Mirzaa GM, Parry DA, Fry AE, et al; FORGE Canada Consortium. De novo CCND2 mutations leading to stabilization of cyclin D2 cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome. Nat Genet 2014;46(5):510–515
54 Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. Am J Hum Genet 2012;90(6):1108–1115
55 Mirzaa GM, Conway RL, Gripp KW, et al. Megalencephaly-capillary malformation (MCAP) and megalencephaly-polydactyly-polymicrogyria-hydrocephalus (MPPH) syndromes: two closely related disorders of brain overgrowth and abnormal brain and body morphogenesis. Am J Med Genet A 2012;158A(2):269–291
56 Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Clinical delineation and natural history of the PIK3CA-related overgrowth spectrum. Am J Med Genet A 2014;164A(7):1713–1733
57 Osterling WL, Boyer RS, Hedlund GL, Bale JF Jr. MPPH syndrome: two new cases. Pediatr Neurol 2011;44(5):370–373
58 Cohen MM Jr. Proteus syndrome review: molecular, clinical, and pathologic features. Clin Genet 2014;85(2):111–119
59 Carpten JD, Faber AL, Horn C, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. Nature 2007; 448(7152):439–444
60 Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med 2011; 365(7):611–619
61 Favus MJ, American Society for Bone and Mineral Research. Primer on the metabolic bone diseases and disorders of mineral metabolism. 6th ed. Washington, DC: American Society for Bone and Mineral Research; 2006
62 Diaz A, Danon M, Crawford J. McCune-Albright syndrome and disorders due to activating mutations of GNAS1. J Pediatr Endocrinol Metab 2007;20(8):853–880
63 Lacerda LdaS, Alves UD, Zanier JF, Machado DC, Camilo GB, Lopes AJ. Differential diagnoses of overgrowth syndromes: the most important clinical and radiological disease manifestations. Radiol Res Pract 2014;2014:947451
64 Oduber CE, van der Horst CM, Hennekam RC. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. Ann Plast Surg 2008;60(2):217–223